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(71) Applicant(s)
The Imperial College of Science,Technology & Medicine

(Incorporated in the United Kingdom)

Sherfield Building, Exhibition Road, South Kensington, LONDON, SW7 2AZ, United Kingdom

(72) Inventor(s)
John Bell

(74) Agent and/or Address for Service
Baron & Warren
18 South End, Kensington, LONDON, W8 5BU, United Kingdom

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(56) Documents Cited
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(54) Dialysis electrode device

(57) A dialysis electrode device with an auxiliary drug addition chamber comprises a tubular body part 1 and a probe part 2. The probe part has two internal dialysis chambers 3,4 which are defined by two hollow semi-permeable dialysis fibres 8,9 joined together along their length by a suitable epoxy resin 10. They are sealed, at their proximal ends, to the adjacent end of the body part 1 and a partition 7 by epoxy resin 11 and, at their distal ends, they are sealed with epoxy plugs 12,13 forming a point with the epoxy joint 10 between the fibres. Electrolyte is supplied to the chamber 3 through an inlet conduit 15 and is removed via an outlet conduit 22, whilst a drug or other chemical fluid may be supplied to the chamber 4 via an inlet conduit 23 and is removed via an outlet conduit 24. Working electrode 16 projects into the chamber, and reference and counter electrodes 17,18 within the body part 1 are electrically coupled to the working electrode by the electrolyte solution. The electrodes are used to provide electrical measurements of a selected dialysate being sampled in the chamber 3 and the effect thereon of the drug or other chemical fluid diffusing into the test matter from the chamber 4. Extra chambers with additionl sets of electrodes may be provided.

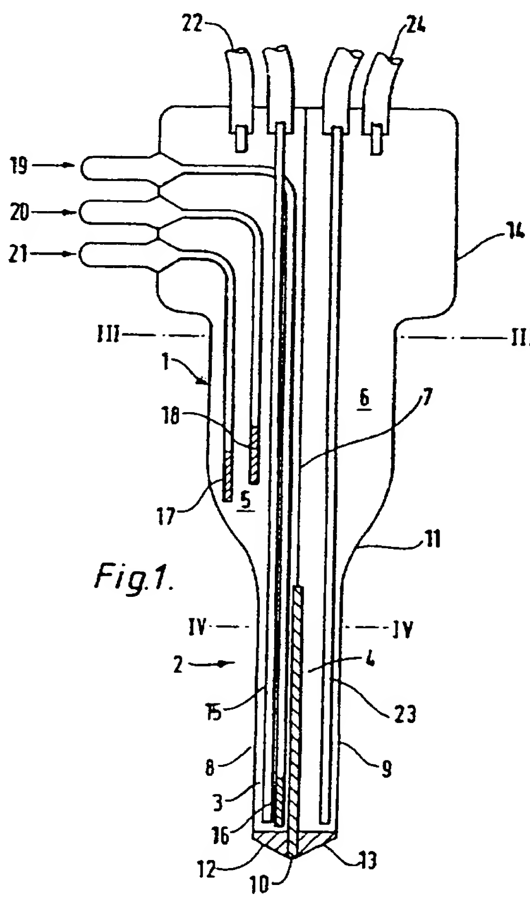

Fig.1.

At least one drawing originally filed was informal and the print reproduced here is taken from a later filed formal copy.

The claims were filed later than the filing date within the period prescribed by Rule 25(1) of the Patents Rules 1995

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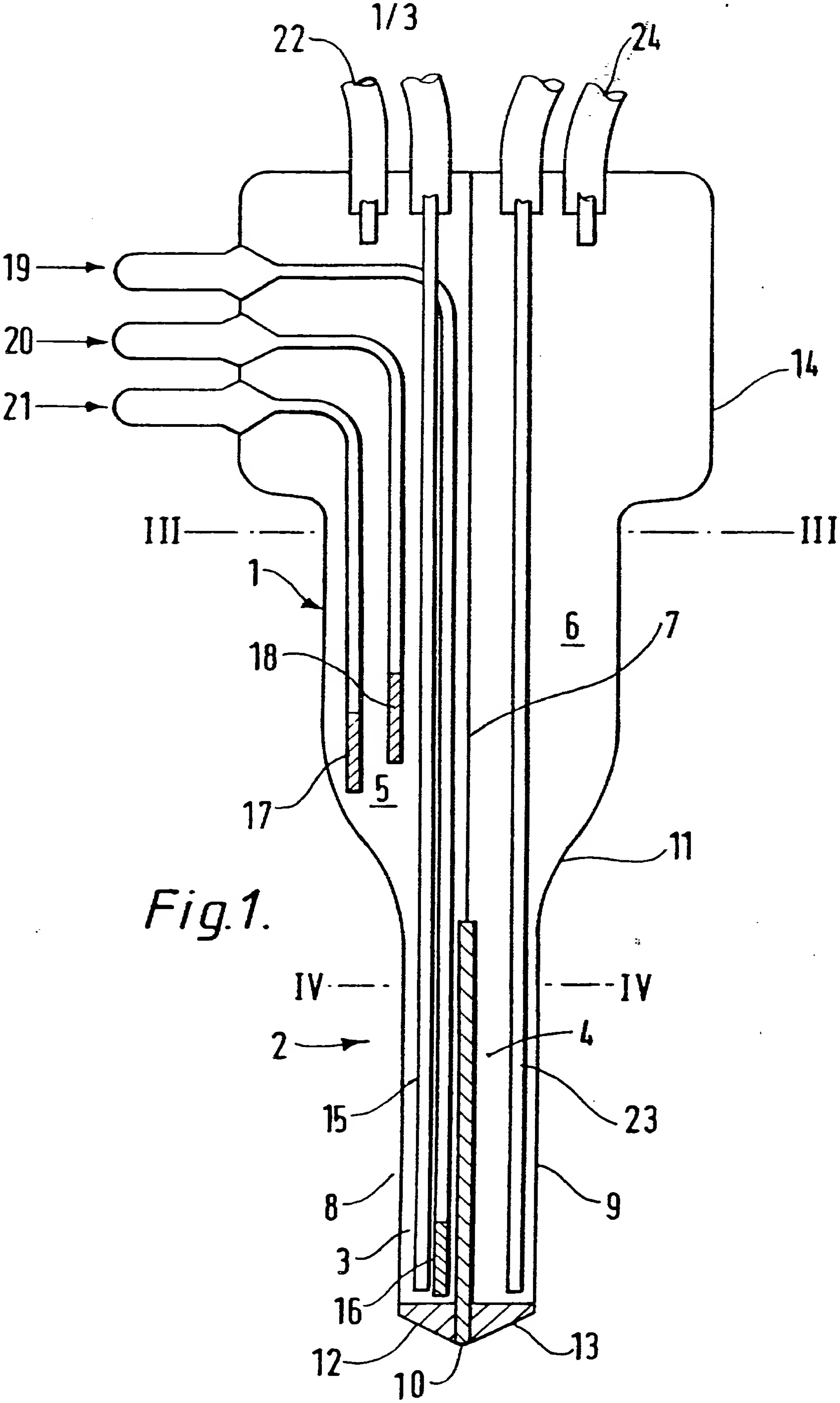

Fig.1.

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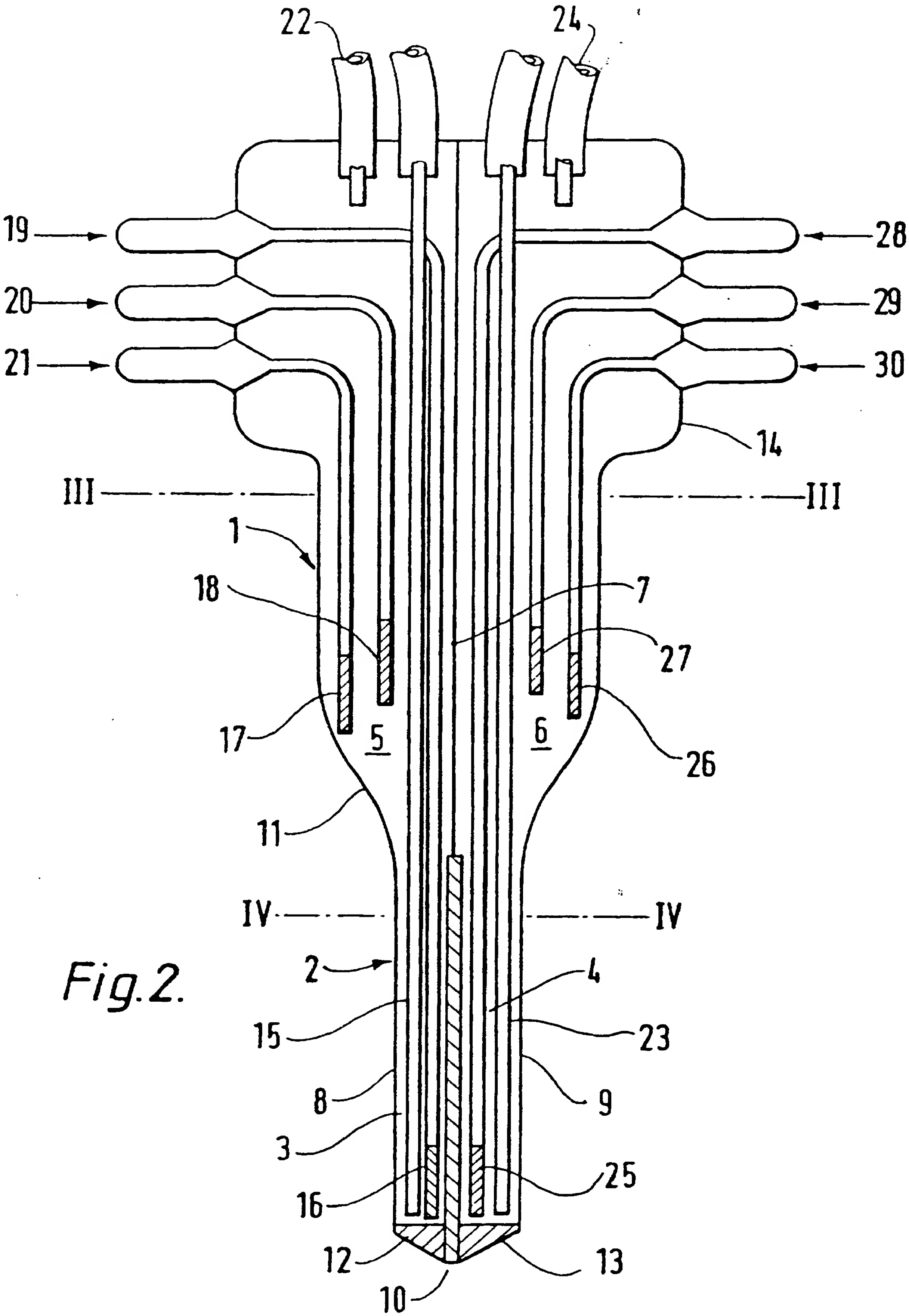

Fig.2.

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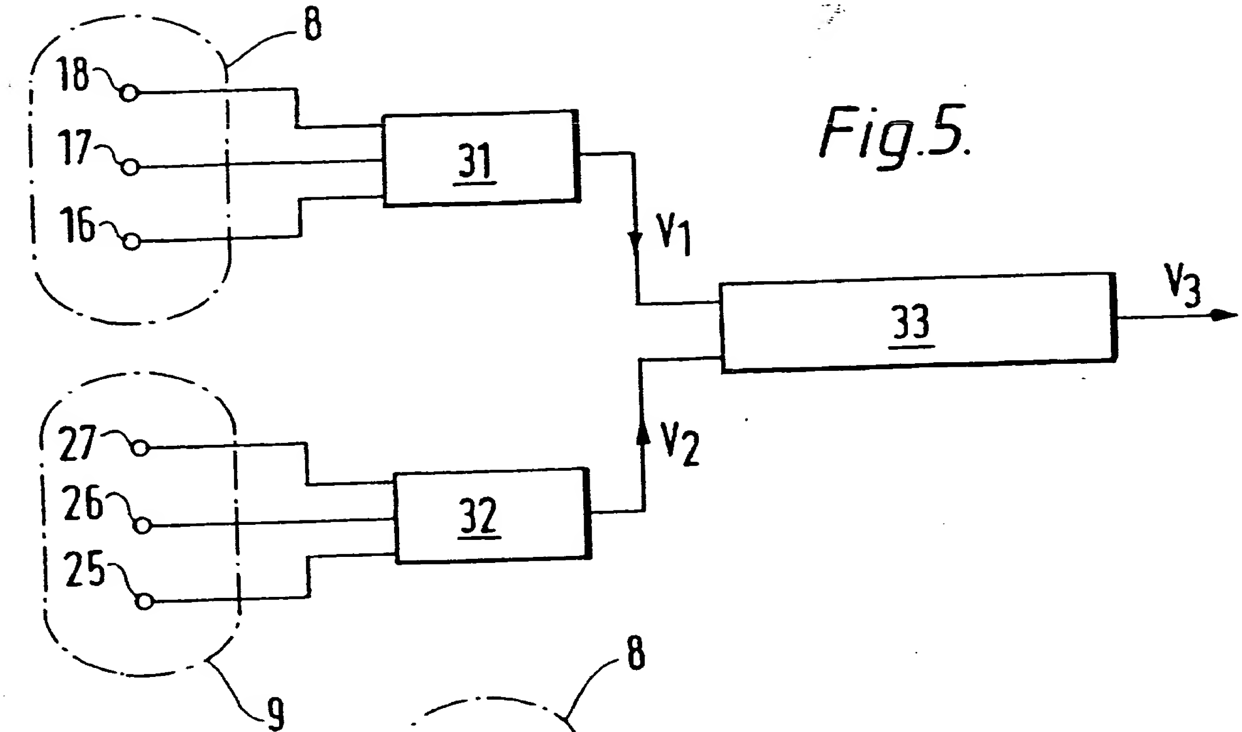

Fig.5.

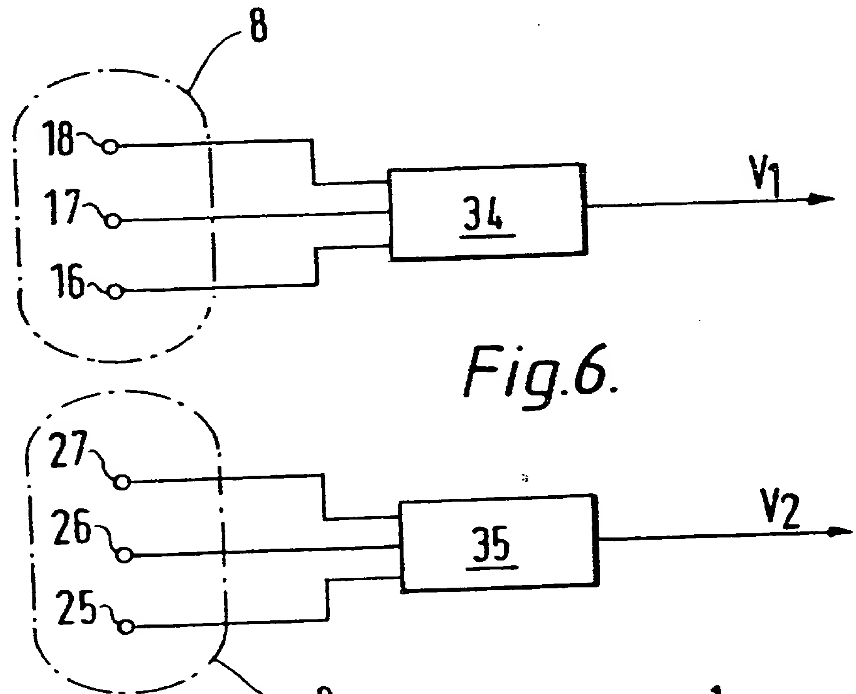

Fig.6.

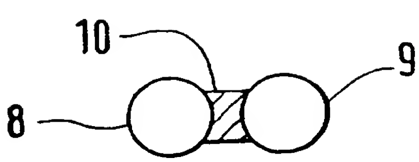

Fig.4.

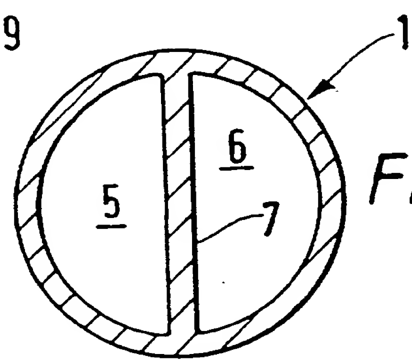

Fig.3.

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DIALYSIS ELECTRODE DEVICE

The present invention relates to a dialysis electrode or biosensor device suitable for use in medicine and the food, drink, pharmaceutical and environmental monitoring fields and other fields where it is desirable to analyze or monitor the presence of chemical substances. More particularly, the invention is directed to improvements in or modifications of the dialysis electrode device described in our prior patent specification WO93/05701.

Dialysis is a general sampling technique which can be used in conjunction with an appropriate analytical technique, such as, electrochemical analysis, to analyze chemical substances recovered by the dialysis. With this technique, a chemical substance diffuses into a dialysis probe, which may be the size of a syringe needle, implanted in tissue or other test matter and the concentration of the substance or dialysate is conventionally determined remotely from the probe. Such conventional dialysis techniques suffer from a threefold problem. Firstly, the dialysate is diluted into a continuous flow of perfusion solution so that relatively large amounts of the dialysate may be removed. Secondly, the technique has a poor time resolution and, thirdly, the continuous removal by dialysis may disturb the concentration of the perfusing species in the region of the probe.

The dialysis electrode device described in our aforementioned specification alleviates these problems and provides a device which is suitable for both *in vitro* and *in vivo* use and which produces rapid measurements of variations in the concentrations of chemical substances. It comprises a hollow probe having an internal chamber and a dialysis membrane forming a wall of the chamber, conduit means for supplying electrolyte solution to the chamber and removing the solution therefrom, a working electrode mounted in the chamber and a reference electrode arranged to be electrically coupled to the working electrode by the electrolyte. The device may be primed intermittently with a flow of the electrolyte solution and electrical measurements of a desired dialysate are made with the probe in situ in organ tissue or other test matter. Measurements are made when there is no flow through the device so that disturbance of the test matter is minimised.

Conventional platinum electrodes may be used or conducting organic salts or other mediators, such as, TTFTCNQ or NMPTCNQ, can be electrochemically plated onto the working electrode. A target molecule, such as a glutamate, diffuses through the dialysis membrane. Instead of being carried away by the flowing solution, it is immediately consumed by the in situ enzyme electrode. Using a dialysis pump connected to the conduit means, the solution around the electrode can be readily changed. This means that the electrode device can be supplied with fresh enzyme and cofactor, as well as different enzyme solutions, thereby enabling the performance of control and test measurements. When the device is not in use all enzyme may be removed to prevent any depletion. The working electrode can also be replated with the same or a different mediator.

Whilst the device described in our aforementioned specification enables different enzyme loaded liquids to be used as electrolyte solutions successively to detect different chemical substances, it would be desirable to provide for the simultaneous measurement of different chemical substances at a test site, as well as permit the monitoring of the reaction of a dialysate to selected chemical substances supplied to the test site. To this end, the present invention has for an object to provide a dialysis electrode device which has improved flexibility in usage.

The present invention consists in a dialysis electrode device comprising a probe having two or more internal chambers, each of which has an external wall formed by a dialysis membrane, and conduit means for supplying electrolyte or other fluid substance to the chambers and removing fluid therefrom, at least one of the chambers having a working electrode mounted in the chamber and a reference electrode arranged to be electrically coupled to the working electrode by the electrolyte.

With the present invention, the or each chamber provided with electrodes is operated in a similar manner to the device described in our aforementioned specification in order to provide electrical measurements of a selected dialysate.

Multiple chambers having electrodes enables the simultaneous measurement of different dialysates or analytes in the same region in real time. Two chambers provided with electrodes enables the simultaneous measurement of a dialysate and the running of a control under identical conditions. Alternatively, they permit differential measurements to be obtained, thereby enabling the subtraction of immediate environmental electrical noise and increase in the sensitivity of the device. Embodiments of the invention in which not all the chambers are fitted with electrodes permit a chamber not so fitted to be used for auxiliary drug addition. There are many uses for such embodiments in pharmacology where the device would, for example, permit the measurement of an analyte to determine the effect of drug addition. The measurement of the analyte can be made in real time whilst simultaneously feeding a drug to the test site. Alternatively, such a device enables analyte measurements to be made in real time whilst simultaneously performing microdialysis.

Preferably, the chambers extend longitudinally of the probe and may be formed, for example, by a plurality of hollow dialysis fibres fixed together in side-by-side relation with their longitudinal axes substantially parallel.

In addition to working and reference electrodes, the or each chamber having these electrodes may be provided with a counter electrode arranged to be electrically coupled to the working electrode by the electrolyte.

In order that the present invention may be more readily understood, reference will now be made to the accompanying drawings, in which:-

Figures 1 and 2 are schematic sectional views of two embodiments of the invention.

Figures 3 and 4 are cross-sections taken along the lines III-III and IV-IV of Figure 1 or 2 and omitting the internal components of the device, and

Figures 5 and 6 are schematic illustrations of measuring circuit which may be used with the invention.

Figure 1 of the drawings illustrates a dialysis electrode device or biosensor with an auxiliary drug addition chamber. The device comprises a tubular body part 1, for example, made from glass, and a probe part 2 projecting from one end of the body part and comprising two internal or dialysis chambers 3,4. The tubular body part 1 is of circular cross-section and is separated internally into two semi-circular auxiliary chambers 5,6 by an integral diametrical partition 7 (see also Figure 3). The internal chambers 3,4 of the probe are defined by two hollow semi-permeable dialysis fibres 8,9 of needle-like configuration which are disposed with their axes substantially mutually parallel and substantially parallel to the axis of the tubular body part. The fibres 8,9 are joined together along their length by a suitable epoxy resin 10 (see also Figure 4) and are sealed at their proximal ends to the adjacent end of the body part and the partition 7 by epoxy resin 11 so that the proximal ends of the passages within the fibres and constituting the internal chambers 3,4 are respectively in communication with the auxiliary chambers 5,6 of the body part. At their distal ends, the fibres are sealed by epoxy plugs 12,13 and the arrangement may be such that the epoxy joint between the fibres and the epoxy plugs form a point at the distal end of the probe.

At its end opposite the probe, the body part 1 is closed by an epoxy housing 14 which also seals the adjacent end of the partition 7 so as to maintain the separate nature of the chambers 3,5 and 4,6. The body part 1 may be fitted with a protective outer sleeve if required.

Projecting axially through the auxiliary chamber 5 of the body part 1 and into the chamber 3 of the hollow fibre 8 is an inlet conduit or cannula 15 for supplying electrolyte solution to the chamber 3. The outlet end of this inlet conduit terminates at a position adjacent the distal end of the fibre 8 and is spaced a small distance from the plug 12. Juxtaposed the conduit 15 is a dialysis or first working electrode 16. A reference electrode 17 and a counter electrode 18 are mounted within the auxiliary chamber 5 and all three electrodes are connected to miniature connectors 19,20,21 sealed through the external side wall of the epoxy housing 14.

Electrolyte solution, such as an enzyme loaded electrolyte solution, supplied to the chamber 3 in the dialysis fibre 8, via the inlet conduit 15, flows from the outlet end thereof through the chamber 3 and about the working electrode 16 and is removed from the device via the proximal end of the chamber 3, the auxiliary chamber 5 and an outlet conduit or cannula 22 at the opposite end of the tubular body part to the probe.

Projecting axially through the body part 1 and into the chamber 4 of the hollow fibre 9 is a second inlet conduit or cannula 23, the outlet end of which terminates at a position adjacent the distal end of the fibre and spaced a small distance above the plug 13. Fluid supplied to the chamber 4 in the dialysis fibre 9 via this inlet conduit is removed from the device by an outlet conduit 24 at the end of the body part opposite the probe 2. The inlet and outlet conduits 15,23 and 22,24 extend through the end wall of the epoxy housing 14 in a sealed manner and are provided with flexible tubing for connecting them to suitable dialysis pumps for supplying and removing fluids from the chambers.

The dialysis fibre 9 serves as an auxiliary drug addition chamber for the probe and in this context a selected drug may be flowed through the chambers 4,6, via the inlet and outlet conduits 23,24, and diffuses into the test site through the wall of the dialysis fibre. This enables the effect of drug addition on the dialysate being sampled in the chamber 3 to be measured.

The second embodiment illustrated in Figure 2, in which like reference numerals indicate similar parts to those of Figure 1, is a dual dialysis electrode device or biosensor. In this second embodiment, working, reference and counter electrodes 25,26,27 are mounted in the chambers 4,6 of the dialysis fibre 9 and the tubular body part 1 in a similar manner to the electrodes 16,17,18. They are connected to miniature connectors 28,29,30 sealed through the wall of the epoxy housing 14. Hence, electrolyte solution may be flowed through the chambers 4,6 via the inlet and outlet conduits 23,24 and the dialysis fibre 9 serves as a second dialysis electrode for the electrical measurement of a particular dialysate diffusing into the fibre.

In addition to permitting the simultaneous measurement of two different dialysates or analytes at the same test site in real time, the embodiment of Figure 2 with its two totally independent dialysis electrodes alternatively permits differential measurements to be obtained which enable the subtraction of immediate environmental electrical noise so as to increase the sensitivity of the device, the simultaneous measurement of the dialysate and running a control under identical conditions, or the differential substraction of interferent signals from other analytes other than the analyte being measured.

Figure 5 schematically illustrates an electrical circuit diagram for producing signals directed to achieving the three, alternative sets of measurements referred to above and comprises two potentiostats 31,32, each having three inputs connected to the working, reference and counter electrodes of one of the dialysis fibres 8,9. The outputs of the potentiostats are connected to the input of a precision differential amplifier 33 which is adapted to reject both DC and AC interference. The output voltage signals V_1 and V_2 of the potentiostats are processed by the amplifier 33 which produces a voltage signal V_3 at its output corresponding to the required measurement.

An electrical circuit for use in the case where the device is used simultaneously to measure the concentrations of two different dialysates in the same region in real time is illustrated in Figure 6. In this case, measurements of the dialysate concentrations may be produced by means of two potentiostats 34,35 having inputs connected to the working, reference and counter electrodes of the dialysis fibres 8,9. The voltage output signals V_1 and V_2 of the potentiostats correspond to the measured concentrations.

The devices described above are suitable for both *in vitro* and *in vivo* use. The length of the probe 2 in either embodiment can be selected so that only the probe, and no other parts of the device, is implanted in organ tissue or other test matter to be analyzed.

Whilst particular embodiments have been described, it will be understood that modifications can be made without departing from the scope of the invention. For example, the external walls of the dialysis fibres 5 may be partially masked, if required.

CLAIMS

1. A dialysis electrode device comprising a probe having two or more internal chambers, each of which has an external wall formed by a dialysis membrane, and conduit means for supplying electrolyte or other fluid substances to the chambers and removing fluid therefrom, at least one of the chambers having a working electrode disposed in the chamber and a reference electrode arranged to be electrically coupled to the working electrode by the electrolyte.

2. A device as claimed in claim 1, wherein at least two of the chambers have working electrodes disposed in the chambers and reference electrodes arranged to be electrically coupled to the associated working electrodes by electrolyte in the chambers so as to permit the simultaneous measurement of different dialysates or analytes in the same region of a test site.

3. A device as claimed in claim 1 or 2, including at least one chamber without electrodes and permitting the addition of a drug or other chemical substance to a test site.

4. A device as claimed in claim 1, 2 or 3, wherein the internal chambers extend longitudinally of the probe.

5. A device as claimed in claim 4, wherein the chambers are formed by one or more hollow dialysis fibres.

6. A device as claimed in claim 5, comprising a plurality of hollow dialysis fibres fixed together in side-by-side relation with their longitudinal axes substantially parallel.

7. A device as claimed in any one of the preceding claims, wherein one or more of the chambers having working and reference electrodes also includes a counter electrode arranged to be electrically coupled to the working electrode by the electrolyte.

8. A device as claimed in any one of the preceding claims, wherein the conduit means for supplying electrolyte or other fluid substance to the chambers comprises an inlet conduit projecting into the associated chamber to a position adjacent the distal end thereof and an outlet conduit communicating with the proximal end of the chamber.

9. A device as claimed in claim 8, wherein the proximal end of each chamber is connected to an auxiliary chamber to which the outlet conduit is connected, and the reference electrode or the reference and counter electrodes are also housed in the auxiliary chamber

10. A dialysis electrode device constructed and adapted to operate substantially as hereinbefore described with reference Figure 1 or 2 of the accompanying drawings in conjunction with Figures 3 to 6.

C1

Application No: GB 9422775.8
Claims searched: 1-10
Examiner: David Mobbs
Date of search: 12 January 1996

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.O): G1N NBPMX, NBPX.

Int Cl (Ed.6): A61B 5/00; G01N 27/49, 33/487, 33/49.

Other: ONLINE: WPI

Documents considered to be relevant:

Category	Identity of document and relevant passage		Relevant to claims
Y	WO 93/05701 A1	IMPERIAL COLLEGE OF SCIENCE TECHNOLOGY AND MEDICINE	1, 2, 4-9.
Y	US 4,834,101	UNIVERSITY OF MICHIGAN	1, 2, 4-9.

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

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